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Sahba Yazdani

Philadelphia College of Osteopathic Medicine, Sahbaya@pcom.edu

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Is Vitamin D Supplementation Effective In Improving Physical Performance In Older Patients With Heart Failure Who Are Over The Age Of 50 Years?

Sahba Yazdani, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements for

The Degree of Master of Science

In

Health Sciences - Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not vitamin D supplement is effective in improving physical performance in older patients with heart failure over the age 50 years

STUDY DESIGN: Review of three English language primary studies, two published in 2010 and one was published in 2013.

DATA SOURCES: Two double blind randomized controlled trials (RCT) and one cross-sectional study that investigated the use of vitamin D in improving physical performance in heart failure. Sources were selected and found using PubMed, ScienceDirect, and Cochrane databases.

OUTCOMES MEASURED: The outcomes measured were improvement of physical performance, and associations among muscle strength, health status measures, and serum vitamin D. Tools used to measure were, a 6 minute walk distance test (6MWD), timed get up and go test (TGUG), isokinetic muscle testing.

RESULTS: The results of two RCT studies Boxer et al. (2013) and Witham et al. (2013) supported that vitamin D does not improve physical performance. The Boxer et al. (2010) cross-sectional study showed no association among serum vitamin D concentration, muscle strength, and health status. Boxer et al. (2013) and Witham et al. (2013) demonstrated that the 6MWD test and TGUG test did not improve with physical activity.

CONCLUSION: The results of the RCT's and the cross-sectional study reviewed; suggest that Vitamin D does not improve the physical performance of older adults with heart failure. This topic does warrant additional research. Further studies conducted should include more frequent, lower doses of vitamin D and examine the results for a longer period of time. The effects of sun-exposure on vitamin D concentration and improvement of physical activity also should be investigated.

KEY WORDS: Vitamin D, Heart Failure, Physical Performance.

INTRODUCTION

Heart failure is identified as an abnormality in heart structure or function leading to inability of the heart to pump blood at an output sufficient to meet requirements of metabolizing tissues or the ability to do so at abnormally elevated diastolic pressures/volume.¹ Average age of patients with heart failure is 76 years in the United Kingdom, with 10% of populations aged ≥ 80 years have heart failure.² The incidence of heart failure increases fourfold between the ages of 65 and 85 years.³ Heart failure is currently the most common cause of hospitalization in the persons in the Medicare age group; more than 70% of the nearly 1 million annual hospitalizations for heart failure involve persons older than 65 years of age.³ Between 1 and 2% of the total health care budget in many developed countries is spent on hospitalizations resulting from heart failure. In 2009, the total cost of heart failure was estimated to be \$37.2 billion in the United States.⁴

Decline in physical function and poor quality of life remains main characteristics of the patients with heart failure. Currently management of patients with heart failure is limited to pharmacology therapy and diet plans to prevent the progression of the disease.¹ Patients with NYHA Class I-III heart failure have benefitted from regular, mild exercises, such as walking or using stationary-bicycles.¹ Despite the therapies available to patients with heart failure, physical functioning remains poor in older adults with heart failure. Several studies; including Boxer et al. (2008) have demonstrated that vitamin D deficiency is associated with reduced physical performance and frailty.⁵ Repletion of vitamin D has shown to result in improvement in strength and balance and reduced risk of falls.⁶ Evidence shows that vitamin D also down-regulates the renin-angiotensin system (RAAS)⁷ and reduces blood pressure,⁷ which both can be of particular importance in patients with heart failure according to the hypothesis that dysregulation of

neurohormonal pathways leads to muscle myopathy.⁶ Heart failure and vitamin D deficiency are both common in older adults.⁸ Therefore, vitamin D supplementation could improve the physical performance in older individuals with heart failure.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not “vitamin D supplementation is effective in improving physical performance in older patients with heart failure who are over the age of 50 years.”

METHODS

The selected articles included men and women with heart failure who were older than 50 years of age. The intervention chosen in the two RCT's was oral vitamin D compared to a placebo. The cross-sectional study examined the association among serum vitamin D, muscle strength and health status. The outcomes addressed included improvement of physical performance, on 6 minute walk distance test (6MWD) and timed get up and go (TGUG). Associations among serum vitamin D concentration, muscle strength, and health status were studied in cross sectional study by measuring vitamin D levels and muscle strength. The types of studies included were two RCTs, and one cross-sectional study.

Key words vitamin D, heart failure and physical performance were searched using the following search engines: PubMed, ScienceDirect, and Cochrane Database. Articles selected were written in the English language, peer reviewed, and published between 2010 and 2013 and had not been previously used in a systematic review or meta-analysis. Inclusion criteria for these studies were RCTs that were published in 2000 or later based on their relevance and importance of the outcome to the patient (Patient Oriented Evidence That Matters, POEMS) and that

investigated the effectiveness of vitamin D in improving physical performance in patients with heart failure (Table 1). Exclusion criteria consisted of studies that investigated patients younger than age 50 years, without a diagnosis of heart failure, patients who were taking daily vitamin D supplements, and patients with a diagnosis of osteoporosis (Table 1). Statistics were reported using mean \pm SD change from baseline, linear regression model, ANCOVA, Pearson X2, Pearson product moment correlation, and p-value

OUTCOMES MEASURED

The outcomes were measured via several different methods. Boxer et al. (2013) measured physical performance at base line and 6 months with the TGUG and 6MWD. TGUG is a reliable and valid test of basic mobility maneuvers, including balance, gait, speed, strength, and functional ability used in measuring clinically significant changes in mobility in older frail patients.² 6MWD has been validated for patients with heart failure; it reflects the type of aerobic activity that older persons with health failure undertake.² Both of these tests are globally used in older individuals to measure basic mobility. They closely mirror the type of aerobic activity that older persons with health failure undertake. Witham et al. (2013) measured physical performance using TGUG and 6MWD. To measure muscle strength, Boxer et al. (2010) used Biodex System 3 Pro Isokinetic Dynamometer. Health status was assessed the by Kansas City Cardiomyopathy Questioner, a 23-item self-administered instrument. Serum analysis was performed by collecting blood, and measuring vitamin D levels by Chemiluminescent Immunoassay.

Table 1 - Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age	Inclusion criteria	Exclusion criteria	W/D	intervention
Boxer (2010)	Cross sectional	40	67.8 \pm 10.9 years	Patients' age \geq 50 with either systolic or preserved systolic function HF. 25OHD concentration \leq 37.5 ng/mL	primary hyperparathyroidism or hypercalcemia; nephrolithiasis; diagnosis of osteoporosis; hemodialysis or peritoneal dialysis and/or creatinine \geq 2.5 mg/dL; current use of daily vitamin D \geq 400 IU, corticosteroids, PTH, androgen, estrogen	0	Association among Serum 25OHD (vitamin D) and muscle strength
Boxer (2013)	Double Blind RCT	64	65.9 \pm 10.4 years	Patients age \geq 50, with HF in class II to IV. Receiving maximum doses of evidence-based HF medication. The required serum 25 (OH)D level \leq 37.5ng/ml.	Primary hyperparathyroidism, sarcoid, hypercalcemia, nephrolithiasis, osteoporosis, creatinine $>$ 2.5 mg/dl, vitamin D supplementation $>$ 400 IU/day	10 – W/D 2- Diseased 64- included in analysis	vitamin D3 50,000 IU daily for 6 months
Witham (2010)	Double Blind RCT	105	aged \geq 70 years	aged \geq 70 years with diagnosed chronic heart failure and 25-hydroxyvitamin D level of $<$ 50 nmol/L	clinical diagnosis of osteomalacia, under investigation for recurrent falls, already taking vitamin D supplements, moderate to severe cognitive impairment	6 due to death 1 ill health 2 other reasons 105- included in analysis	100,000 U of oral vitamin D2 at baseline, 10 weeks, and 20 weeks

RESULTS

The three articles presented in this review had continuous data, which could not be converted to dichotomous data. In the study done by Boxter et al. (2013), the reported statistics compared oral vitamin D supplement to placebo. The results of the TGUG and 6MWD, were calculated for vitamin D (n=31) group, and placebo group (n=33) as mean \pm SD, at baseline and 6 months (Table 2). The treatment effect, (vitamin D versus placebo) was evaluated at each end point by ANCOVA model as frequencies and proportions for categorical variables within study groups. In TGUG and 6MWD, the differences in physical function improvement between the vitamin D group and placebo group were 0.8 and 20, respectively.⁶ The results did not reach a statistically significant value, $p=0.30^6$ (TGUG) and $p=0.80^6$ (6MWD) (Table 2).

Table 2 - Change in Aerobic Capacity and Muscle Strength in the vitamin D and Placebo Groups

End point	<u>6-Month change in endpoint</u>		<u>ANCOVA model</u>	
	Vitamin D (=31)	Placebo (n=33)	Vitamin D – Placebo Difference	p value
TGUG baseline to 6 mo	-.02 \pm 3.3	-1.0 \pm 3.3	0.8	0.30
6MWD (m) Baseline to 6 mo	59 \pm 282	36 \pm 228	20	0.80

Values are mean \pm SD. ANCOVA= analysis of covariance

In the study performed by Witham et al. (2013) statistics reported; compared vitamin D supplement to placebo. Differences between groups were compared at baseline versus 10 weeks, and base line versus 20 weeks. Pearson X^2 test was used to compare categorical variables. Of the participants in the placebo group (n=52), 46 (88%) completed 6MWD test at the end of week 10th, compared with 45 (85%) in the treatment group (n=53). In the 6MWT, a change of 30 m in distance is the minimum required to show clinical improvements.² The between group difference at baseline versus 10 weeks showed no significant improvement. -2.4 (95% confidence interval [CI], -17.1 to 12.4); ($p=0.75$).² (Table 3). At 20 weeks, 42 participants in each group (81% in

placebo and 79% in vitamin D group) were able to complete the 6MWD. Unadjusted analysis (Table 3) and adjusted analysis (for key variables at baseline) showed no improvement with vitamin D supplementation $p=0.51^2$ in unadjusted analysis (Table3) and $p=0.68^2$ in adjusted analysis. Also outcomes on TGUG showed no improvement with vitamin D supplementation² (Table 3). The score of TGUG at 10 weeks and 20 weeks showed no significant improvement in function either. At week 10, the between group difference was 0.21 (CI -1.79 to 1.37); ($p= 0.80$), and at 20 weeks, the between group difference was 1.42 (CI -1.13 to 3.97); ($p=.27$); (Table 3).²

Table 3- Changes in Outcome Measures

	<u>0 VS. 10 weeks</u>		<u>0 VS. 20 weeks</u>	
	Between- group Difference (95% CI)	p	Between- group Different (95% CI)	p
6-min, m	-2.4(-17.1 to 12.4)	0.75	-5.6(-22.2 to 11.0)	0.51
TGUG, s	0.21(-1.79 to 1.37)	0.80	1.42(-1.13 to 3.97)	0.27

In the last study, Boxer et al. (2010) assessed the association among serum vitamin D concentrations (a level of ≤ 0.05 was considered significant), physical performance, and health status. A linear regression model then studied the association after adjusting for other potential variables.⁷ The mean serum vitamin D concentration was 18.5 ± 9.1 ng/m.⁷ The levels varied by race, with African Americans having the lowest (16 versus 22 ng/ml, $p=0.4$). Muscle strength was measured by weight bearing ability in flexion, with men having a mean ($n=18$) of 17.1 ± 6.7 , and women ($n=21$) of 16.1 ± 6.1 .⁷ There was no association between serum vitamin D concentration and muscle strength.⁷ Data showed, “Older age trended toward significance at $p=0.08$, with older age relating to lower peak torque.”⁷ The mean total score on Kansas City Cardiomyopathy Questionnaire (KCCQ) was 68.9 ± 22.9 .⁷ There was also no association between KCCQ total score and serum vitamin D concentrations. However, there was an

association between serum vitamin D levels and physical limitation scores, which is one of the four domains of KCCQ ($r=0.32$, and $p=0.04$)⁷. However, after data were adjusted for African Americans (with lowest score) and New York Heart Association (NYHA), (lower class of heart failure had highest score), the association was lost.⁷

In the two RCT's, control groups were vitamin D groups. However, in the cross-sectional study there was no control group, and association between three variables was studied. Each study had specific inclusion/exclusion criteria. They all included patients in NYHA functional Class II to IV who were 50 years of age or older. Boxer et al. (2010) and Boxer et al. (2013) excluded patients who were taking daily vitamin D supplements of > 400 IU and with a diagnosis of osteoporosis. Witham et al. (2013) excluded any patient who was taking any daily dose of vitamin D and those with a current diagnosis of osteopenia.

In Boxer et al. (2013) study, six patients from the control group and six patients from the placebo group did not complete the trial.⁶ One patient in each group died and five in each group withdrew.⁶ The monthly pill counts showed 100% compliance in the vitamin D group and 99.5% in the placebo group.⁶ Witham et al. (2013) reported, the death of two patients in each group before completion of Week 10, and another two deaths in control group before Week 20. One individual dropped of the control group because of ill health before Week 20. One patient in the placebo group violated the protocols and was dropped between Week 10 and 20 and one other patient in the placebo group moved away between Week 10 and 20 and thus dropped out.¹ To ensure adherence, a research nurse directly observed each patient take the pill in the participant's own home.¹ Adherence was reported 100% throughout.”¹

Both the Boxer et al. (2013) and Witham et al. (2013) studies showed interventions were well tolerated.^{2, 6} Boxer et al. reported no significant difference between the control group and the placebo group with the exception of increasing numbers of infections in the vitamin D group (18 compared to six).⁶ Witham et al. (2013) reported an increase of creatinine of greater than 25% in five patients in the vitamin D group compared to one patient in the placebo group ($p=0.11$).²

DISCUSSION

The results from Boxer et al. (2013) and Witham et al. (2013) studies, showed physical performance in older patients with heart failure did not improve by vitamin D supplementation.^{2,6} Boxer et al. (2010) found no association between the serum vitamin D concentrations and muscle strength.⁷ The studies performed contained some factors that may have affected the outcome results. Boxer et al. (2013) used a diverse study population with strong presentation of women.⁶ Witham et al. (2013) study included a large sample size however, it underrepresented women.⁷ On the other hand, Witham et al. states “30 m is the minimum clinically important improvement”² 6MWT. Also the subsequent narrow CI around the 6MWT “makes it unlikely that any clinically significant effect were missed in Witham study.”² Such result is in agreement with the findings of studies investigated in this paper.

Result from the study of vitamin D effects in older individuals without a diagnosis of heart failure with vitamin D insufficiency, showed some benefits in physical performance after treatment with vitamin D.⁸ Small and frequent dose of 800 to 1000 IU/day of vitamin D, and specifically combined with calcium has shown benefits in the results of TGUG but not 6MWD.⁷ Boxer et al. (2013) study used high dose of vitamin D₃ with calcium as intervention. It is

possible that a smaller, more frequent dose of vitamin D₃ might be beneficial in improvement of physical performance in older patients with heart failure. Witham et al. (2013) did not use any calcium with the vitamin D administration.²

Outcomes in the Boxer et al. (2013) and Witham et al. (2013) studies could be different if therapy was continued for a longer period of time. A longer duration therapy with the vitamin D could elicit changes in physical function.^{2, 6} Boxer et al. (2010) study was limited by cross-sectional design due to the fact that it only studied association between variables. Sample sizes in Boxer et al. (2013) and Boxer et al. (2010) were too small.^{6, 7} A larger sample size could lead to different outcomes in both studies. Boxer et al. (2013) explains that it is theorized vitamin D reduces the risk for infection and inflammations,⁶ however the most significant adverse event in this study was the higher number of infections in vitamin D group compared to the placebo group,⁶ “This might be due to small sample size or to multiple comparisons.”⁶ Witham et al. (2013) study used vitamin D₂ (because it was the largest dose of oral vitamin D available). Vitamin D₃ has a greater peak levels and longer half-life, therefore results in Witham et al. (2013) could be different if vitamin D₃ was used as intervention.²

Vitamin D supplements are readily available over the counter in United States. Vitamin D is thought to be important for maintaining normal function of tissues such as muscle (including heart muscle), immune function, and inflammation.¹ The U.S. National Academy of Science recommends 800 IU vitamin D/day from food and supplement.¹ Vitamin D intoxication is rare but it can cause hypercalcemia.¹

CONCLUSION

The results of the RTC's studies suggested that vitamin D does not improve the physical performance in the older adults with the heart failure. The cross-sectional study indicated there is no association between serum vitamin D levels and muscle strength.

Future studies should be conducted with Vitamin D treatment starting at the earliest stage of HF to determine whether increasing Vitamin D concentration to an optimal level will prevent progression of HF and manifestation of physical functioning decline. In addition further studies should be conducted with lower doses and more frequent doses of vitamin D with conjunction of including a larger sample size.

Boxer et al. (2010) points out to the importance of sun-exposure in maintaining the serum concentration level of vitamin D.⁷ Patients with heart failure have limited mobility ability and therefore might be deprived from sun-exposure. Future studies are warranted to investigate the relation of sun-exposure to serum concentration level of vitamin D and its effect on physical performance in patients with heart failure.

References

1. Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson J, Loscalzo J. eds. *Harrison's principles of internal medicine*. New York : McGraw-Hill, 2012; 18th ed; 2012.
<http://ezproxy.pcom.edu:2048/login?url=http://search.ebscohost.com.ezproxy.pcom.edu:2048/login.aspx?direct=true&db=cat00201a&AN=pcom.34729&site=eds-live&scope=site>.
2. Witham MD, Crichton LJ, Gillespie ND, Struthers AD, McMurdo MET. The effects of vitamin D supplementation on physical function and quality of life in older patients with heart failure a randomized controlled trial. *Circulation: Heart Failure*. 2010;3(2):195-201. doi: 10.1161/CIRCHEARTFAILURE.109.907899.
3. Williams BA, Chang A, Ahalt C, et al.. *Current diagnosis and treatment [electronic resource] : Geriatrics / [editors] brie A. williams, MD, MS ; anna chang, MD ; cyrus ahalt, MPP ; rebecca conant, MD ; christine ritchie, MD, MSPH ; helen chen, MD ; C. seth landefeld, MD ; michi yukawa, MD, MPH*. New York : McGraw-Hill Education, 2014]; Second edition; 2014.
<http://ezproxy.pcom.edu:2048/login?url=http://search.ebscohost.com.ezproxy.pcom.edu:2048/login.aspx?direct=true&db=cat00201a&AN=pcom.42376&site=eds-live&scope=site>; <http://ezproxy.pcom.edu:2048/Login?url=http://accessmedicine.mhmed.ical.com.ezproxy.pcom.edu:2048/book.aspx?bookid=953>.
4. Hurst JW, Fuster V, Walsh RA, Harrington RA. *Hurst's the heart / editors, valentin fuster, richard A. walsh, robert A. harrington ; associate editors, sharon A. hunt ... [et al..]*. New York : McGraw-Hill Medical, c2011; 13th ed; 2011.
<http://ezproxy.pcom.edu:2048/login?url=http://search.ebscohost.com.ezproxy.pcom.edu:2048/login.aspx?direct=true&db=cat00201a&AN=pcom.34770&site=eds-live&scope=site>.
5. Boxer, Rebecca S.Dauser, Deborah A.Walsh, Stephen J.Hager, W. DavidKenny,Anne M. The association between vitamin D and inflammation with the 6-minute walk and frailty in patients with heart failure. *J Am Geriatr Soc*. 2008;56(3):454-461. doi: 10.1111/j.1532-5415.2007.01601.x.
6. Boxer RS, Kenny AM, Schmotzer BJ, Vest M, Fiutem JJ, Piña IL. A randomized controlled trial of high-dose vitamin D3 in patients with heart failure. *JACC: Heart Failure*. 2013;1(1):84-90.
doi:<http://dx.doi.org.ezproxy.pcom.edu:2048/10.1016/j.jchf.2012.11.003>.
7. Boxer RS, Kenny AM, Cheruvu VK, Vest M, Fiutem JJ, Piña II. Serum 25-hydroxyvitamin D concentration is associated with functional capacity in older adults with heart failure. *Am Heart J*. 2010;160(5):893-899.
doi:<http://dx.doi.org.ezproxy.pcom.edu:2048/10.1016/j.ahj.2010.08.004>.

8. Zhu, KunAustin, NicoleDevine, AmandaBruce, DavidPrince,Richard L. A randomized controlled trial of the effects of vitamin D on muscle strength and mobility in older women with vitamin D insufficiency ZHU ET AL. EFFECTS OF VITAMIN D ON MUSCLE STRENGTH AND MOBILITY. *J Am Geriatr Soc.* 2010;58(11):2063-2068. doi: 10.1111/j.1532-5415.2010.0314.